Plasma Neuropeptide-Y Concentrations in Humans Exposed to Military Survival Training

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Background: *Neuropeptide-Y (NPY) is present in extensive neuronal systems of the brain and is present in high concentrations in cell bodies and terminals in the amygdala. Preclinical studies have shown that injections of NPY into the central nucleus of the amygdala function as a central anxiolytic and buffer against the effects of stress. The objective of this study was to assess plasma NPY immunoreactivity in healthy soldiers participating in high intensity military training at the U.S. Army survival school. The Army survival school provides a means of observing individuals under high levels of physical, environmental, and psychological stress, and consequently is considered a reasonable analogue to stress incurred as a result of war or other catastrophic experiences.*

Methods: *Plasma levels of NPY were assessed at baseline (prior to initiation of training), and 24 hours after the conclusion of survival training in 49 subjects, and at baseline and during the Prisoner of War (P.O.W.) experience (immediately after exposure to a military interrogation) in 21 additional subjects.*

Results: *Plasma NPY levels were significantly increased compared to baseline following interrogations and were significantly higher in Special Forces soldiers, compared to non-Special Forces soldiers. NPY elicited by interrogation stress was significantly correlated to the subjects' behavior during interrogations and tended to be negatively correlated to symptoms of reported dissociation. Twenty-four hours after the conclusion of survival training, NPY had returned to baseline in Special Forces soldiers, but remained significantly lower than baseline values in non–Special Forces soldiers. NPY was positively correlated with both cortisol and behavioral performance under stress. NPY was negatively related to psychological symptoms of dissociation.*

Conclusions: *These results provide evidence that uncontrollable stress significantly increases plasma NPY in humans, and when extended, produces a significant depletion of plasma NPY. Stress-induced alterations of plasma NPY were significantly different in Special Forces soldiers compared to non–Special Forces soldiers. These data support the idea that NPY may be involved in the enhanced stress resilience seen in humans.* Biol Psychiatry 2000;47:902–909

Key words: Military stress, stess resilience, PTSD, Special Forces, cortisol

Introduction

Neuropeptide-Y (NPY) is a 36-amino acid peptide that has been highly conserved throughout mammalian evolution. It belongs to the pancreatic polypeptide family, is co-localized (and released) with neurons containing norepinephrine, and is intimately involved in the regulation of both central and peripheral noradrenergic system functioning. Over the past decade, a growing body of preclinical and clinical evidence suggests that in addition to its involvement in the maintenance of vascular tone and appetite, NPY functions as an endogenous anxiolytic agent that may buffer against the effects of stress on the mammalian brain.

In rats exposed to anxiety-provoking paradigms (such as the elevated plus maze test, the conflict test, and fear-potentiated startle), NPY agonists produce behavioral responses similar to those produced by compounds, such as benzodiazepines, that are anxiolytic in humans (Broqua et al 1995; Heilig et al 1992). In addition, NPY administration by the i.c.v. route has been shown to effectively prevent stress-induced gastric ulceration (Heilig and Murrison 1987). By contrast, when expression of the NPY Y1 receptor subtype is inhibited by central administration of an antisense oligodeoxynucleotide, behavioral signs of anxiety are elicited (Wahlestedt et al 1993). Further, local injections of a selective NPY Y1 agonist indicate that the anxiolytic action of NPY may be mediated by Y1 receptors in the amygdala (Heilig et al 1993)—a neuroanatomic structure critical to the emotions of fear and anxiety.

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In humans, increases in circulating NPY levels have been found in response to several stress conditions, such as 75% V02 max exercise—the point at which the cells of the body reach 75% of their maximum ability to consume oxygen (VO2 max; Lundberg et al 1985), exercise with hypoxia (Kaijser et al 1990), the cold pressor test (Morris et al 1986), and in response to noradrenergic activation produced by the α-2 receptor antagonist yohimbine (Rasmusson et al 1998). Of note, investigators have not found increased NPY to mild types of stress, such as mental tasks, head-up tilt, or mild exercise (Lundberg et al 1985; Morris et al 1986; Pernow et al 1986).

Reductions of cerebrospinal fluid (CSF) levels of NPY have been reported in individuals suffering from major depression (Widerlov et al 1988), and in suicide victims (Widdowson et al 1992). More recently, reductions in plasma NPY have been detected in combat veterans with and without combat-related posttraumatic stress disorder (Rasmusson et al 2000). Additional clinical support for the anxiolytic role of NPY in humans may be found in the strong negative correlation reported between anxiety scores and CSF NPY levels in patients suffering from depression (Heilig et al 1990).

The current study was part of a larger investigation examining the effects of uncontrollable stress on several neuroendocrine and psychological indices of soldiers participating in the U.S. Army's survival training course. This training is among the most difficult and rigorous in the U.S. Armed Forces. The U.S. Army survival course prepares soldiers for the demands of independent survival in hostile environments and attempts to reduce their vulnerability to captivity-based experiences.

Several factors make survival training an ideal environment to study the effects of acute and unavoidable stress: First, the design and schedule of the training permits NPY assessment during a stable, low-stress, baseline phase, during a high-stress phase that ensures a uniform application of the various stressors across subjects, and during the low-stress recovery day; second, survival training provides an ethologically realistic model of acute, uncontrollable stress that closely approximates combat stress as well as preclinical models of uncontrollable stress. As we have reported elsewhere (C.A. Morgan et al, unpublished data) the stress experienced by soldiers participating in the captivity phase of survival training is intense and produces significant alterations in neuroendocrine responding as measured by cortisol, testosterone, and thyroid indices. In response to the intense psychological stress of simulated captivity, glucocorticoids levels significantly increase and are greatest after exposure to psychological interrogations. For example, serum cortisol levels measured during interrogation stress (33.6 μg/dL, or the equivalent of 927 nmol/L) are equal to, or greater, than those measured in individuals undergoing major surgery (717 nmol/L; Parker et al 1985), continuous and exhausting physical exercise corresponding to 35% V02 max (731 nmol/L; Opstad 1992), flying military aircraft (221 nmol/L; Leedy and Wilson 1985; Leino et al 1995), or skydiving (450 nmol/L) (Chatterton et al 1997). As we have previously reported, the alterations in cortisol are observed in the absence of physical activity and in response to the psychological stress of interrogation. The current report addresses effects of such stress on plasma NPY in a cohort of soldiers (n = 49) tested prior to, and 24 hours after completion of survival training, and in a second cohort of soldiers (n = 21) who were tested prior to and during exposure to survival training.

Methods and Materials

Seventy of 75 consecutively recruited active-duty male soldiers (age 27.8 years, SD = 5), were the subjects of this study. As designated by their military operational specialty, 32 subjects were non-Special Forces (non-SF), and 38 subjects were special forces (SF). The methodology employed in this study has been reported elsewhere (C.A. Morgan et al, unpublished data); however, a brief summary will be provided. Prior to enrollment in this investigation, each participant completed in-processing into the Army survival training course. Recruitment of subjects was conducted by the principal investigator (CAM) at the U.S. Army John F. Kennedy Special Warfare Training Center and School, Fort Bragg, North Carolina. All subjects gave written, informed consent. As per survival training course requirements, all subjects provided documentation of physical examination and medical clearance within 30 days of enrollment. All subjects were free of illicit substances. Five subjects declined to enroll in the study. They did not differ as a group (in terms of age, rank, or military operational specialty) from those who did enroll. Each stated that he did not enroll owing to a concern that information from the research might somehow be documented in their military records. Each appeared to be worried that such information, if inadvertently included in their military records, might jeopardize their subsequent evaluations. Because of Army restrictions limiting the number of blood draws, the subjects of this study (n = 70) are divided into two subgroups. Those in the first subgroup (n = 49) were sampled at baseline and at recovery; subjects in the second subgroup (n = 21) were sampled at baseline and during exposure to stress.

Baseline Assessment

Baseline blood samples were collected in 70 subjects at the survival training facilities, Fort Bragg, North Carolina. For all subjects, these were obtained at 17:00 hours on the second day of classroom educational activities, and five days prior to the stress assessment.

Stress Samples

At the conclusion of the didactic phase of the training, soldiers entered the experiential phase of the survival course. During this

phase, the soldiers were given, in as highly a realistic manner as possible, a captivity experience in the Army's training laboratory (TL). In the TL, each subject was subjected to intense and uncontrollable stress, and each attempted to avoid exploitation by their captors. Because of the classified nature of the course, a detailed description of the individual stressors is not possible. To facilitate an interpretation of the current data, however, the following comments are in order: First, the challenges to subjects in the TL are modeled from those experienced by American captives in WWII, Korea, and Vietnam. Broadly speaking, these include interrogations and problem-solving dilemmas designed to test their ability to utilize and adhere to their training and a prescribed code of conduct. NPY stress samples were obtained in 21 soldiers within 12 hours of captivity and immediately after exposure to their first military interrogation in the TL. Cortisol levels were obtained as a measure of activation of the stress axis. Prior to their interrogation, each subject remained seated and alone in an isolation room for approximately 4 hours. Next, subjects were escorted to the interrogations, where each remained standing and relatively immobile for the 50 minutes of interrogation. No subject engaged in physical activity other than standing or leaning against the wall during the interrogations. All subjects were food deprived for 12 hours prior to the interrogation. In addition, no subjects were sleep deprived prior to the interrogation time point. Thus, within the context of this naturalistic investigation, the interrogation permitted a realistic assessment of the plasma concentrations of NPY in soldiers during exposure to acute stress.

As part of their evaluation of each participant, survival instructors (professional military interrogators) created an "interrogation behavior score." The score was the sum of *observed*, classified, target behaviors that survival students are expected to demonstrate. These behaviors have been identified by the Army and the Joint Services Survival, Evasion, Resistance, and Escape Agency (JSSA), as ones that are most likely to enhance a soldier's success in surviving interrogation by the enemy. Participant demonstration of target behaviors is a clear indication to the interrogators of an individual's ability to maintain effective engagement with the "hostile" situation and to demonstrate sustained efficiency in "cognitive operations" under interrogation stress. The use of the term "cognitive operations" by interrogation specialists refers to a person's ability to interact with the interrogator and to incorporate new information provided in the interrogation setting. The behavioral scores reflect these abilities and are recorded by instructors at the conclusion of their interrogation of each student. These scores were created independently from the research team, and as such provide a naturalistic "double-blind" rating, or measure of performance as judged by military experts. A total score of 15 was possible. Behavioral scores were only available for the subgroup of subjects whose NPY was assessed immediately at the conclusion of the stress of interrogation ($n = 21$).

Recovery Samples

Twenty-four hours after their release from the TL, recovery blood samples were collected in 49 subjects. While in the TL, and after their interrogation stress, all subjects experienced sleep deprivation. All subjects were subjected to the same level of sleep deprivation. During the 72-hour experience, subjects were permitted to sleep for a total of 19 minutes. In addition to sleep deprivation, all subjects were subjected to uniform food deprivation. All were monitored by the medical staff at the TL and all received water on a uniform scheduled manner. No subject refused fluid intake. At the time of release from the TL, each subject was given a sack lunch containing the same contents (sandwich, cookies, and an apple). All subjects were confined to the barracks compound and did not leave until the completion of the recovery day debriefing. On recovery day, no subject participated in physical exercise and all received the same breakfast and lunch. All participated in a classroom debriefing and none ate between lunch and the recovery assessment (5 hours).

At the recovery assessment, all study subjects completed a reliable and valid self-report questionnaire designed to assess the occurrence and severity of dissociative symptoms experienced by the soldier (Clinician-Administered Dissociative States Scale [CADSS]; Bremner et al 1998). Each was instructed to complete the CADSS in reference to his TL interrogation experience. The items on the scale are designed to assess how perceptually "in touch" (or out of touch) an individual is vis-à-vis the environment following exposure to conditions that are highly stressful. Whereas some of the items on the scale asks about one's sense of physical self (e.g., "Do you feel as if you are looking at things outside of your body?", "Do you feel as if you are watching the situation as an observer or spectator?"), others ask about cognitive or perceptual distortions (e.g., "Do colors seem to be diminished in intensity?", "Do sounds almost disappear or become much stronger than you would have expected?", "Do you space out or in some way lose track of what is going on?" "Do you see things as if you were in a tunnel, or looking through a wide-angle photographic lense?"). The self-report scale contains 19 items, each of which is rated by subjects on a likert-type scale of 0 (not at all) to 4 (extremely). A total score of 76 is possible.

Serum NPY Analysis Methods

Plasma was stored at −70° C from the time of initial collection. NPY was measured after plasma extraction using a double antibody radioimmunoassay (RIA) using [125I]-NPY as the tracer. This RIA possesses an assay sensitivity of 20 pg/mL and intra-and inter-assay coefficients of variation of 8% and 10%, respectively (Allen et al 1991). Displacement of [125I]-NPY from NPY antiserum 3-5 by NPY analogues using this method has been reported elsewhere (Allen et al 1991). Percent binding of NPY and NPY 2-36 to [NPY]-α-globulin 3-5 is 100% and 100%, respectively (Allen et al 1991).

Serum and Salivary Cortisol

Serum was collected as described above. Saliva was collected in Salivette tubes (Sarstedt, Newton, NC), centrifuged and pipetted into two 1.5 mL plastic vials. The samples were shipped on dry ice to our laboratory and stored at − 70° C until assayed. Serum and salivary cortisol were analysed by RIA procedures (Incstar

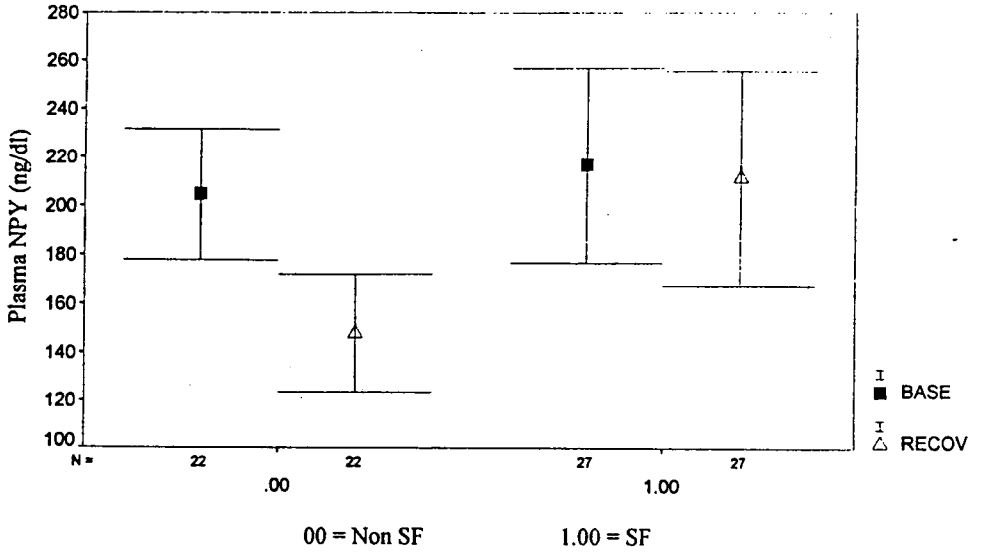

Figure 1. Plasma neuropeptide-Y (NPY) at baseline and at recovery. In the group of subjects (n = 49) tested at baseline and at recovery (24 hours after the conclusion of uncontrollable stress), analysis of variance revealed significant, within-subject, Time (baseline/recovery) and Group × Time (SF/non-SF) effects (F[1,47] = 6.0; $p < .01$; F[1,47] = 4.1; $p < .04$, respectively). Neuropeptide-Y was significantly reduced in the non-SF (df = 21, t = 3.6; $p < .002$) but not the SF soldiers (df = 47, t = 0.5; $p < .6$). Independent t test comparisons of baseline NPY did not show any group differences (df = 47, t = .5; $p < .6$). SF, Special Forces.

Corp., Stillwater, MN). The inter-assay coefficient of variation in our laboratory is 6.1%.

Data Analysis

Separate repeated-measures analyses of variance (ANOVAs) using factors "Time" (baseline/recovery; baseline/stress) and "Group" (SF/non-SF) was performed for each of the two cohorts of subjects. A general linear model procedure was used to compute each ANOVA in order to account for the discrepancies in sample size. Post-hoc comparisons were made using least square means also to adjust for the slight differences in the number of subjects for each group (baseline/stress: 10 vs. 11 subjects; baseline/recovery: 22 vs. 27 subjects).

Independent t tests were also performed between the baseline serum hormone values of the larger sample (n = 49) and those of the subsample (n = 21) in order to determine whether the baseline NPY values of the smaller group (n = 21) were representative of the larger group (n = 49). The independent t tests were first examined for homogeneity of variance between the SF and non-SF samples. No differences were found between the groups according to Levene's Test for Equality of Variances. Equal variances were revealed and appropriate ts and degrees of freedom are reported.

Pearson correlation analyses were used to evaluate the relationship between NPY and independent variables, such as Age and Weight, evaluate the relationship between NPY and cortisol at the respective plasma collection timepoints (baseline, stress, recovery), compare NPY values during interrogation stress and the subjects' corresponding interrogation-related behavioral scores, and finally, to compare NPY values during interrogation stress to the CADSS dissociation scores reported 24 hours after the conclusion of survival training. Finally, in the larger group (n = 49), Pearson correlation analyses were also used to compare dissociation scores and NPY values at recovery.

Results

No significant relationships were found between the independent variables Age and Weight and plasma NPY values at baseline, during stress, or at recovery. Therefore, these variables were removed from subsequent analyses.

In the group of subjects tested at baseline and at recovery, a repeated measures ANOVA conducted on the NPY values for each time point (baseline/recovery) and for each group (SF/non-SF) revealed a trend toward a statistically significant effect of Time (F[1,47] = 3.0; $p <$ .09). ANOVA, however, revealed a significant within-subject effects for factor Time (F[47] = 6.0; $p < .01$) and a significant Group × Time interaction (F[47] = 4.1; $p <$ .04). This was owing to the fact (as shown in Figure 1) that NPY values of SF and non-SF soldiers differed significantly 24 hours after survival training stress. Post-hoc paired t tests revealed that, although neuropeptide-Y was significantly reduced, compared to baseline, in the non-SF soldiers (df = 21, t = 3.6; $p < .002$), it was not significantly reduced in the SF soldiers (df = 26, t = .28; p = .8). Independent t test comparisons of baseline neuropeptide-Y did not show any group differences (df = 47, t = .5; $p < .6$).

In the group of subjects tested at baseline and immedi-

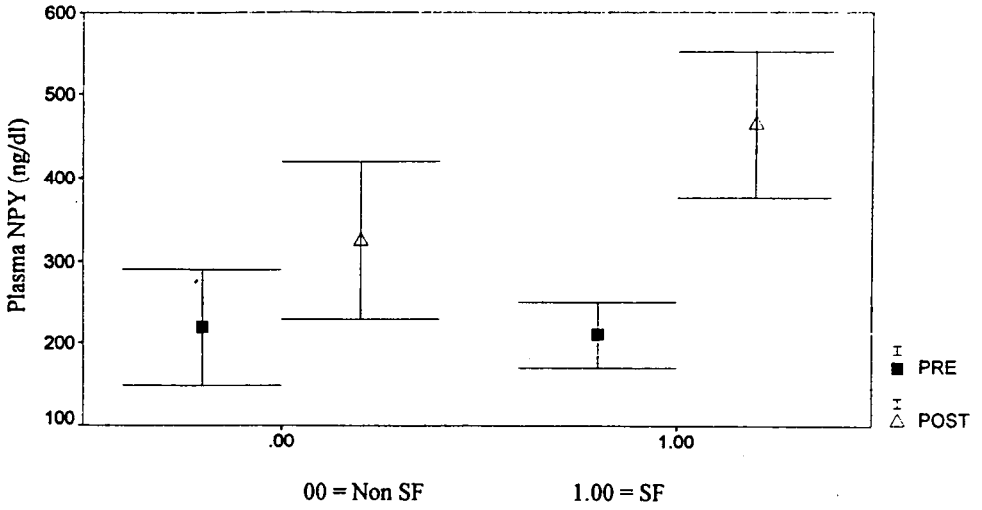

Figure 2. Plasma neuropeptide-Y (NPY) at baseline and during acute stress. In the group of subjects (non-SF group, $n = 10$; SF group, $n = 11$) tested at baseline and during phase of uncontrollable stress, analysis of variance revealed significant, within-subject, Time (baseline/stress) and Group × Time (SF/non-SF) effects ($F[1,19] = 48.4; p < .0001$; $F[1,19] = 7.3; p < .02$, respectively). Acute stress significantly increased NPY in subjects, however the stress-induced increase in NPY was significantly greater in SF soldiers (df = 19, $t = 2.65; p < .02$). Independent t test comparisons of baseline NPY did not show any group differences (df = 19, $t = .9; p < .4$). SF, Special Forces.

ately after exposure to interrogation stress, a repeated measures ANOVA using factors Time (baseline/stress) and Group (SF/non-SF) revealed that there was no significant overall effect of Time ($F[1,19] = 2.8$; $p < .1$); however, there was a significant within-subject effect for factor Time ($F[1,19] = 48.4$; $p < .0001$) as well as a significant Group × Time interaction ($F[1,19] = 7.3; p < .02$). As shown in Figure 2 , post-hoc paired t tests revealed that although neuropeptide-Y was significantly increased in non-SF (df = 10, $t = 3.3; p < .01$) and in SF soldiers (df = 10, $t = 5.9; p < .0001$), post-hoc independent t tests revealed that NPY values were significantly greater in the SF group compared to the non-SF group after interrogation stress (df = 19, $t = 2.65$; $p < .02$). Independent t test comparisons of baseline neuropeptide-Y did not show any SF/non-SF differences (df = 19, $t = .9$; $p < .4$).

As shown in Figure 3 , Pearson correlation analyses revealed a significant, positive relationship between the levels of NPY elicited by interrogation stress and the interrogation behavior score ($r = .45$; $p < .04$). Pearson correlation analyses of the dissociation scores and the levels of NPY during stress exposure indicated a trend toward a significance for the group as a whole ($r = -.41$; $p < .09$). Because of the significant Group × Time effect (noted above), Pearson correlation analyses were conducted on the SF and non-SF groups separately. These revealed a significant, negative relationship between dissociation scores and stress-induced plasma levels of NPY for the SF group only ($r = -.56; p < .02$). No significant relationship was observed between dissociation scores and NPY values obtained at recovery for the larger group ($n = 49$).

As shown in Figure 4 , there was a significant correlation between NPY and cortisol during stress ($r = 0.67$; $p < .001$). There was also a significant correlation between *change* in NPY and *change* in cortisol during stress ($r = 0.73; p < .0001$). No significant relationships were observed between NPY and cortisol at baseline or at recovery.

Discussion

The current data provide robust evidence that exposure to acute, uncontrollable stress significantly affects levels of circulating plasma NPY in humans. NPY was significantly increased by the acute psychological stress of military interrogation and significantly reduced in a subset of individuals 24 hours after the cessation of stress. The present findings also indicate that individuals differ significantly in their NPY response to stress. In both the large group ($n = 49$) and the small group ($n = 21$), NPY values of non-SF and SF soldiers did not differ at baseline. When tested immediately after exposure to acute stress, however, SF soldiers had significantly greater levels of NPY compared to non-SF soldiers. In addition, 24 hours after the completion of survival training, NPY levels in SF soldiers had returned to baseline, whereas those of non-SF soldiers were significantly below baseline values.

NPY increased in response to interrogation stress. This

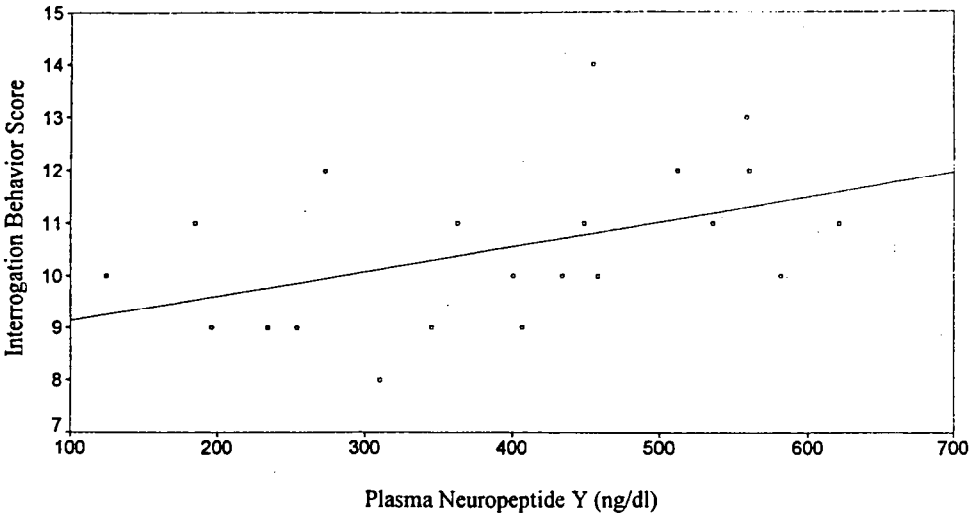

Figure 3. Relationship of neuropeptide-Y to observed behavior during interrogation stress. Pearson correlation analyses revealed a significant, positive relationship between the levels of neuropeptide-Y elicited by interrogation stress and the behavior score assigned by survival instructors during the interrogation ($r = .45$; $p < .04$).

increase in NPY occurred in the absence of physical exertion and coincided with a robust increase in salivary and serum cortisol (reported elsewhere, C.A. Morgan et al, unpublished data). To our knowledge, this is the first report of significant increases in plasma NPY of humans exposed to acute psychological stress. Further, the elevations of NPY in response to interrogation stress are equal to, if not greater than, those observed in humans receiving intravenous administration of the α-2 receptor antagonist yohimbine (Rasmusson et al 1998). Within the central nervous system, neuronal structures intimately involved in the fear/alarm response (such as the amygdala, the locus coeruleus, the hippocampus, and the bed nucleus of the stria terminalis) have dense networks of NPY fibers (Heilig et al 1990). Centrally, NPY is co-localized and co-released from many noradrenergic cell neurons in these sites. Threatening stimuli would be expected to activate central neuronal noradrenergic activity in the locus coeruleus and potentially lead to an increase in the central release of NPY (Illes and Regenold 1990; Kopin et al 1983). Preclinical studies examining the effects of centrally administered NPY agonists suggest that this stress-induced release of NPY may, acting at Y1 receptors, exert an anxiolytic effect (Britten et al 1997; Heilig et al 1992, 1993). Thus, individuals with greater increases of NPY release in response to stress might experience less subjective distress and remain more interactive with their environment. The fact that SF soldiers had higher levels of NPY, were rated by military interrogators as exhibiting greater mental alertness (as indicated by the behavioral scores) during interrogation stress, and reported significantly fewer symptoms of dissociation compared to non-SF soldiers supports this conceptualization. Further, in light of preclinical evidence showing that NPY may modulate memory retention (Flood et al 1989; Nakajima et al 1994), it is possible that SF soldiers may, if tested, exhibit superior performance on memory tasks during stress, compared to non-SF soldiers. To date, this possibility remains unexplored.

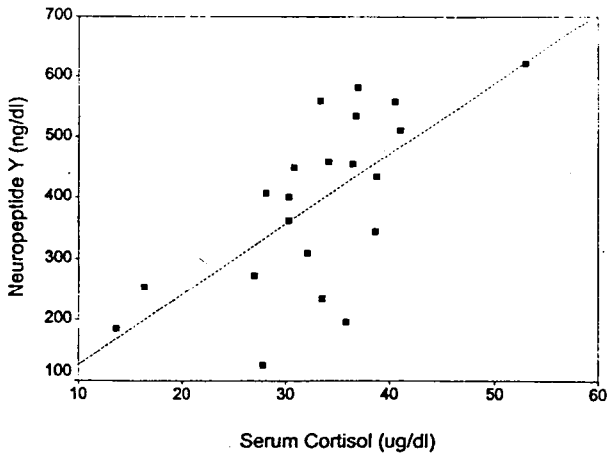

Figure 4. Neuropeptide-Y and cortisol during stress. Pearson correlation analyses of neuropeptide-Y levels during stress exposure and serum cortisol levels during stress exposure indicated a significant, positive relationship for the group as a whole ($r = .67$; $p < .001$).

NPY was significantly reduced, compared to baseline values in non-SF soldiers 24 hours after the conclusion of survival training. This suggests that NPY levels may be depleted by prolonged exposure to high-intensity stress in

a subset of individuals. To our knowledge this is the first direct report demonstrating a significant acute stress-induced reduction of NPY in humans (Corder et al 1992). A possible mechanism for this depletion is enhanced, stress-induced clearance of NPY. Preclinical studies have provided evidence that 125I-NPY clearance markedly increases during stress, and that the mechanisms involved in such clearance may include a receptor mediated internalization of NPY or protease-mediated enyzymatic degradation (Torda et al 1988; Zukowska-Grojec et al 1993).

Special Forces soldiers are identified by the Army as being more "stress hardy" than most other soldiers. The fact that these individuals have, compared to non-SF subjects, a more robust NPY response to stress, and regain baseline NPY values within 24 hours post stress exposure is noteworthy. Whether such differences in NPY are predominantly peripheral, central, or both, they support the idea that NPY may be involved in the enhanced adaptation to, and recovery from, stress that has been traditionally observed in SF soldiers. Preclinical studies have provided evidence that the expression of NPY is upregulated by stress (Zukowska-Grojec et al 1993); therefore it is possible that these soldiers differ from others in their ability to upregulate NPY.

In the periphery, NPY is present in noradrenergic perivascular, cardiac enteric, and parasympathetic nerves, as well as in the adrenal medulla (Jahng et al 1997). It is often, but not always, co-localized in sympathetic neurons (Wahlestedt et al 1993). Among its many roles, one of the more well-characterized is NPY's direct and indirect enhancement of vasoconstriction via NPY Y1 receptors (Wahlestedt et al 1993). The reciprocal enhancement of blood vessel hypersensitivity to NPY by stress-induced release of catecholamines strongly implicates its intimate involvement in the "stress-response."

The current study has several limitations. First, this study assessed peripheral blood levels, and not central nervous system levels of NPY. The exact nature of the relationship between central and peripheral measures of NPY is poorly understood at this time. There is evidence that the relationship is approximately 2:1 (Dotsch et al 1997); however, given that so little is actually known about it, the current data permit only inferences about central NPY activity. The abundant co-localization of NPY with norepinephrine-releasing cells in the brain and in the periphery, coupled with the fact that both central and peripheral norepinephrine release is increased by stress, do support the idea that there may be a positive relationship between central and peripheral NPY responding (Kopin et al 1983). At this time, it has not been established whether central and peripheral NPY are a common system that responds similarly to stress.

Second, the TL experience involved multiple types of stress. In addition to powerful psychological stress, subjects were food and sleep deprived during their captivity experience—both of which may have affected levels of NPY (Ehlers et al 1997; Kaye et al 1990; Stanley et al 1985). It is unlikely, however, that either satisfactorily accounts for the current findings, because sleep deprivation and food deprivation were uniformly applied across subjects and, as a result, cannot account for the differences in NPY values between SF and non-SF soldiers. Moreover, the effect of food deprivation would be expected to produce an *increase* in NPY, whereas a significant reduction was observed at the recovery time point in non-SF soldiers. Third, the dissociation measures were collected 24 hours after the conclusion of survival school training and may be influenced by recall bias.

A large body of evidence suggests that NPY is a neurotransmitter and neurohormone intimately involved in the body's stress responses. The current finding of enhanced NPY responses to acute stress in individuals recognized as "stress hardy" may represent a step toward improving our understanding of the various factors that contribute to stress resilience and stress vulnerability in humans. The current data underscore the potential therapeutic benefits of NPY agonists in humans—an issue that may be clarified by investigating the effects of NPY agonists in the treatment of individuals suffering from anxiety and stress-related disorders.

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